



## LET US ASCEND THE WALL AGAINST DENGUE (THE DISEASE OF POVERTY)

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### ABSTRACT

The origin of the word dengue is not clear. It is believed "Cramp like seizure caused by evil spirit". In Spanish, dengue were said to have the posture and gait of a dandy, and the disease was known as "Dandy Fever". Benjamin Rush, Coined the term "Break bone fever" because of the symptoms of myalgia and arthralgia.

260 peer-reviewed articles referred to dengue as "Poor man's disease". It is a severe life-threatening disease. "Dengue is a mosquito-borne infection caused by a flavivirus".

Dengue fever is continuous or "saddleback" with a break on 4<sup>th</sup> or 5<sup>th</sup> day and then recrudescence; usually lasts 7-8 days. Classical dengue fever is characterized by the onset of fever, malaise, headache, facial flushing, retro bulbar pain that worsens on eye movements, conjunctival suffusion and severe back ache, which is a prominent symptom. Lymphadenopathy, petechiae on the soft palate and transient morbilliform skin rashes may also appear on the limbs with subsequent spread to involve the trunk. Desquamation occurs. Cough is uncommon. Dengue fever syndrome is characterized by capillary leak syndrome, thrombocytopenia, hemorrhage, hypotension, and shock. It is characteristically a disease of children occurring most commonly in South-East Asia. Over 100 million cases occur every year in the tropics with over 10,000 deaths from dengue hemorrhagic fever. Previously, dengue was seen in small children and DHF/DSS in children 2-15 years old, and most frequently in those 16-45 years of age or older in whom severe organ dysfunction is more common. Other epidemiological changes include the spread of dengue into rural communities and greater case fatality in women.

Like malaria epidemic, dengue fever epidemics depend on temperature. Dengue and chicken guinea are two important viruses causing febrile illness syndrome.

**KEYWORDS:** Desquamation, Thrombocytopenia, Hemorrhage, Hypotension, Intracutaneous Langerhans cells, Apoptosis, Fluorescent antibody, Vasculopathy, Thrombopathy.

### INTRODUCTION:

There are 4 types of dengue viruses. (DEN 1,2,3, and 4) and the presence of antibody directed against one type does not give cross-protection against the other three, worse still is the fact that antibodies can enhance the infection of peripheral blood mononuclear cells by Fc-receptors, mediated uptake of the antibody-coated dengue virus particle. (1)

These dengue agents are widespread throughout the world particularly the Middle East, and the Caribbean islands. The characteristic illness usually results in fever, erythematous rash and severe pain in back, head, muscles, and joints. (2)

The dengue fever, leading to shock, organ impairment and bleeding complications. (3)

Diagnosing of arthropod borne viral infections (Arboviruses) has been a challenge for decades as dengue viruses (DENVs) and other flaviviruses and alpha viruses have expanded their global reach. Serological detection of infection is complicated by the cross reactivity of antibodies induced by these viruses as well as the fact that frequent serial infections with related viruses provoke anamnestic recall responses to the primary infection. The recent introduction and use of DENV vaccine is likely to further complicate serological analysis of acute infection (4) Dengue serology is complicated by 4 antigenically related serotypes as well as other related flaviviruses, whereby cross-reactive serological responses may be stimulated by infection or vaccination. (5)

Dengue manifests as high fever, severe headache, arthralgias, myalgias and sometimes a rash. Patients with dengue hemorrhagic fever suffer from bleeding phenomena and circulatory failure. (6)

Standard serological differentiation of acute (DENV) infection using immunoglobulin M(IgM) and IgG(IgG) assays demonstrated high false positive rates, particularly in vaccinated individuals. (7)

Dengue remains a major public health problem worldwide and the virus has been described as one of the most important arthropod borne disease viruses. (8)

The distinction from yellow fever may require geographic data, clinical features, and virologic studies. Immunohistochemical demonstration of the virus within

hepatocytes has been described (9)

The fever ailment, dengue fever (DF) is prevalent in sub-tropical and tropical countries with over 3.9 billion people being at risk of dengue virus infection worldwide. (10)

Recent studies have estimated that possibly more than half of the world population is at risk of dengue virus (DENV (11,12))

Dengue is mainly transmitted by Aedes Aegypti, an urban adapted mosquito widely distributed in tropical and subtropical regions of the world. (13,14)

A recent study demonstrated successful invasion of Wallachia infected mosquitoes into natural mosquito population in Australia (15)

Serological assays detecting anti dengue immunoglobulin M (IgM) or immunoglobulin G (IgG) antibodies, with or without dengue non structural protein 1 (NSI) antigen detection are widely used for dengue diagnosis. Seroprevalence analysis and disease surveillance as such tests are user friendly and affordable. However the utility of these serological assays may be confounded by dengue vaccination as IgG and IgM levels may reflect vaccine-induced responses. (16)

The impact of dengue vaccination on the serological diagnosis of dengue in larger and more diverse epidemiological settings of 2 phase 111 CYD-TDY efficacy studies. (17)

WHO has evidence for a continuing reduction in mortality, attributed in part to use of bed nets and combination drug therapies. (18,19)

In most extreme cases, so much internal hemorrhaging results into dengue shock syndrome (DSS). DSS is frequently fatal. (20)

Biological control strategies using mosquito predators, such as guppy fish, are used in some countries such as Cambodia and Philippines. (21)

### History:

It is not clear where the word "dengue" came from. Some people think that it comes from the Swahili phrase Ka-dinga pepo. This phrase talks about the dis-

ease being caused by an evil spirit. The Swahili word dinga is thought to come from the Spanish word dengue, which means "careful." That word may have been used to describe a person having bone pain from dengue fever; that pain would make the person walk carefully.[34] However, it is also possible that the Spanish word came from the Swahili word, and not the other way around (22)

Dengue fever is probably a very old disease. An ancient Chinese medical encyclopedia from the Jin Dynasty (which existed from 265 to 420 AD) talked about a person who probably had dengue. The book talked about a "water poison" that had to do with flying insects.

Written records from the 17<sup>th</sup> century talk about what may have been epidemics of dengue (where the disease spread very quickly in a short time). The most likely early reports of dengue epidemics are from 1779 and 1780. These reports talk about an epidemic that spread across Asia, Africa, and North America. From that time until 1940, there were not many more epidemics. (23)

In 1906, scientists proved that people were getting infections from *Aedes* mosquitoes. In 1907, scientists showed that a virus causes dengue. This was just the second disease that was shown to be caused by a virus. (The first was yellow fever.)[ John Burton Cleland and Joseph Franklin Siler kept studying the dengue virus, and figured out the basics of how the virus spreads. (24)

An intrinsic incubation of 3-8 days in human, an extrinsic incubation period of 8-11 days in mosquitoes, immunity in people and monkeys and the non susceptibility of most domestic animals were demonstrated in the classic studies of Silver and Simmons and their coworkers. (25)

Other people think that the name "dengue" comes from the West Indies. In the West Indies, slaves that had dengue were said to stand and walk like "a dandy." Because of this, the disease was also called "dandy fever". (26)

The name "breakbone fever" was first used by Benjamin Rush, a doctor and United States "Founding Father." In 1789, Rush used the name "breakbone fever" in a report about the 1780 dengue outbreak in Philadelphia. In his official report, Rush mostly used the more formal name "bilious remitting fever". (27)

Scientists also keep working on creating antiviral drugs to treat attacks of dengue fever and keep people from getting severe complications. (28)

They are also working on figuring out how the virus's proteins are structured. This may help them create medications that work well for dengue. (29)

Dengue happens most around the equator. 2.5 billion people live in areas where dengue happens. 70% of these people live in Asia and the Pacific. (30)

In the United States, 2.9% to 8% of people who come back from traveling in areas where dengue happens, and have a fever, were infected while traveling.[14] In this group of people, dengue is the second most common infection to be diagnosed, after malaria (31)

Primary dengue virus infection and epidemics were common in North America, the Caribbean, and Australia during the 18<sup>th</sup> and 19<sup>th</sup> centuries, presumably due to the wider ecology of the mosquito vectors. During the world war, 11 DENV spread to and through South East Asia. Troop movement and the destruction of the environment and human settlements are believed to have promoted the spread of DENV and their mosquito vectors throughout South Asia and Western Pacific. Indeed after a recent outbreak in West Florida in 2009 a serosurvey conducted by the centers for disease control and Prevention (CDC) reported that recent DENV infection has increased 500 folds, with more than a hundred countries affected by outbreaks of dengue. (32)

Most people who get the dengue virus (80%) have no symptoms, or have only mild symptoms (like a basic fever) About 5% of infected people (or 5 out of every 100) get much sicker. A small number of these people have symptoms that could kill them. (33)

#### Significant gap in research:

According to WHO, the incidence in human has increased within the past 3 decades and within 24 hrs infectious diseases can erupt just about anywhere in the world. Infectious diseases has stimulated the establishment of systemic epidemiology. (34)

Higher temperatures increase the rate of larval development and accelerate the emergence of adult *Aedes* mosquitoes. (35)

#### Major advances and discoveries:

Infection by these arboviruses causes involvement of several organs, especially the liver. Severe liver involvement is one of the important risk factors in patients who die from infection with severe Dengue and Yellow fever. (36)

In humans, dengue viruses infect and replicate efficiently in intracutaneous Langerhans cells, where infection produces apoptosis, but such cells may not

serve as replicative hosts. Late infection, viral antigen is found associated with circulating B lymphocytes. (37)

A fluorescent antibody, virus isolation, electron-microscopic, and in situ hybridization studies suggest mononuclear phagocytes as major infection hosts. (38)

Evidence shows that the liver is an important organ of replication and pathogenesis of infection by DENV and YFV, although its mechanisms are not yet fully understood. Therefore, further studies are needed to elucidate the exact mechanisms of liver tissue damage. (39,40)

In contrast to other encephalitis viruses JEV, WNV, Tick-borne encephalitis viruses, DENV, historically has not been considered as neurotropic. However, the discovery of DENV and anti-DENV IgM in the cerebrospinal fluid of the patients with encephalopathy suggests that it may be capable of causing CNS infection as part of severe DHF/DSS at least in a subset of individuals. In support of this focal imaging abnormalities have been detected in brain MRI scans of DENV infected patients although these results are suggestive, bonafide DENV encephalitis and CNS disease may not be fully accepted until its antigens are reliably detected in the brains of encephalopathic patients and a more complete understanding of the molecular determinants for neurotropism is required.

#### Clinical features:

Classical dengue fever usually affects older children and adults. It is followed by fever, headache, and pain in muscles and bones. The fever is biphasic (Saddle-back) Incubation period is 5-8 days. The maculopapular rash generally appears on 3 or 4 days. The febrile illness lasts for about 10 days. The dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) remains mostly confined to children of 5-10 years age. It is seen in patients previously infected with the dengue virus. Dengue fever is continuous or "saddleback" with a break on 4<sup>th</sup> or 5<sup>th</sup> day and then recrudescence; usually lasts 7-8 days.

#### Diagnosis:

Rapid flow ICT assays available for the qualitative detection of anti DENV IgM, IgG, IgA, and NSI Antigen in human blood require minimum time, technical expertise and infrastructure. (41)

The detection capability of these assays for different viral markers varies in different geographical settings. Hence there is a need to evaluate these ICT assays with a reference test for detecting clinically apparent DENV infections. A standard ELISA is commonly used as a comparator to evaluate rapid assays. (42)

Laboratory features include leucopenia, neutropenia, thrombocytopenia, elevated alanine aminotransferase (ALT) or Aspartate aminotransferase (AST). Many symptomatic infections run an uncomplicated course but complications or protracted convalescence may ensue. Warning signs intense medical management and monitoring for progression to serve dengue. Atypical clinical features of dengue are increasingly common, especially in infants or older patients these along with DHF or DSS. The diagnosis can be confirmed by sero conversion of IgM or a four-fold rise in IgG antibody titres. Serological tests may detect cross-reacting antibodies from infection or vaccination against other flaviviruses including yellow fever virus, Japanese encephalitis virus, and West Nile virus. Detection of dengue virus RNA by PCR in blood or CSF is available in special laboratories. (43)

ELISA is used for the detection of IgM antibody. A strip of an immunochromatographic test for IgM is also available for rapid diagnosis. IgG antibody appears later than IgM titer in paired sera taken at an interval of ten days or more is confirmatory.

ELISA is used for detection of IgG antibody. Immunochromatographic test is available for detection of NSI antigen. It is a rapid test and detects antigen on the first day of fever before antibody appears. It takes 15 minutes for isolation of the virus. (44)

#### Treatment:

The presence of clinically apparent dengue virus (DENV) infection has increased significantly in recent decades. Since there is no specific treatment to dengue virus, patients are solely managed by supportive therapy. More over prevention of dengue is challenging for health authorities despite the exhausting efforts taken in the dengue endemic countries including Sri Lanka. Though the recombinant tetravalent vaccine (Dengvaxia) registered for use in Mexico in 2015. (45)

Treatment is supportive. Paracetamol is the preferred antipyretic agent. Mild sedation is required to control pain. Fluid replacement and appropriate management of shock and organ dysfunction, which is a major determinant of morbidity and mortality. With intensive care support, the mortality rate is 1% less. Aspirin should not be given due to bleeding risk. Glucocorticoids have not been shown help. No existing antivirals are effective.

#### Prevention:

The mosquito-borne viral disease dengue has become one of the worst nightmares of the country. The fever of dengue can attack anyone but those with weaker immunity are more prone to the disease getting severe when they are

attacked. Dengue is caused by the bite of one of the many types of mosquitoes in the genus *Aedes Aegypti*, which has white stripes on their bodies and legs. It is caused when the mosquito has previously bitten a person who was infected. Control of stagnant water using mosquito nets is highly useful in malaria control but *Aedes aegypti* bites during the day. The ability to predict epidemics and to put in practice public health and clinical needs to deal with such surges in demand would be a major advance with ongoing difficulties in the development of an effective and balanced vaccine to all four dengue serotypes; concerted efforts are needed to address this important global health threat. (46)

### CONCLUSION:

The occurrence of recurring outbreaks every 3–5 years with an increasing number of cases over time shows the transition from an endemic-epidemic state to a highly endemic state in recent years.

Dengue remains to be an important health problem affecting geographies, across the globe. Few serotypes are more dangerous. Rapid diagnosis and serotyping remains the key for better patient management and prevention of disease spreading in the community. Highly sensitive, specific and rapid CDC real time PCR assay. It is a promising tool among all available molecular diagnostic methods. (47)

The only control measure currently available is vector control, but this method has proven difficult to maintain over time. The implementation of the IMS-dengue has contributed to an integrated response to outbreaks; however, all its components should be strengthened. Additional control measures such as the development of effective tetravalent vaccines, more modern vector control programs, and full implementation of the IMS-dengue are needed to reduce the disease burden in the coming years. (48)

### Challenges:

Dengue begins suddenly, with more benign symptoms at first but which may get severe with time. Dengue is one of the world's most important emerging diseases as the global incidence continues to rise and new areas of the world experience explosive epidemics, there are major challenges ahead. There have been recent advances in our understanding of the immunopathogenesis and pathophysiology plus identification of the therapeutic targets, which should lead to urgently needed treatments. The development of an effective and safe vaccine to all four dengue serotypes and better control of the vector are needed to address this important and growing global health threat.

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